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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/390,634	09/07/99	PRICE	P 0942.4190002

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EXAMINER	
KERR, J	
ART UNIT	**PAPER NUMBER**
1633	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/390,634	Price et al.
Examiner	**Group Art Unit**
Janet M. Kerr	1633

☒ Responsive to communication(s) filed on *Sep 7, 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *89-126* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *89-126* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The preliminary amendments, filed on 9/7/99 and 12/21/99, have been entered.

Claims 1-88 have been canceled.

Claims 89-126 are being examined on the merits.

Information Disclosure Statement

The statement of facts, submitted in the Information Disclosure Statement, filed on 12/21/99, has been reviewed and considered.

Specification

The use of the trademark "AlbuMax" has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

Claims 125 and 126 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 125 recites "wherein said isolating further comprises isolating said protein from said embryonic stem cells" and claim 126 recites "wherein said isolating further comprises isolating said protein from said harvested medium". However, the claim upon which claims 125 and 126 depend, i.e., claim 124 contains the limitation of "isolating said protein from said embryonic stem cells or from the medium in which said cells are cultured". Thus, claims 125 and 126 do not further limit claim 124. Applicants should delete the term "further" in claims 125 and 126 to overcome this rejection.

Claim 97 is objected to because of the following informalities: the phrase "are obtained from mouse" should be changed to "are obtained from mice" or "are obtained from a mouse". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 89-126 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of culturing murine embryonic stem cell lines in a serum-free medium composition comprising the specific nutrients and ranges of nutrients recited in the preferred embodiments of Tables 1-3, as set forth in Examples 1-5, and compositions comprising said embryonic stem cells and said medium, does not reasonably provide enablement for methods of culturing any embryonic stem cell, in the absence of a feeder layer, and with any serum-free culture medium, compositions comprising any embryonic cell with any serum-free medium formulation, methods of differentiating embryonic stem cells under serum-free conditions, methods of obtaining embryonic stem cells from blastocysts using serum-free culture conditions, or methods of producing recombinant proteins using embryonic stem cells under serum-free conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 89, 91, and 105-107 are directed to methods of expanding embryonic stem cells in serum-free culture. Claims 108-116 are directed to methods for controlling or preventing the differentiation of embryonic stem cells in serum-free culture. Claims 117-121 are directed to methods of differentiating embryonic stem cells into a particular cell type. Claims 122 and 123 are

directed to methods of obtaining embryonic stem cells in serum-free culture. Claims 124-126 are directed to methods of producing recombinant proteins in embryonic stem cells in serum-free culture.

Claims 91-97 are directed to compositions comprising embryonic stem cells in a serum-free medium.

Claims 98-104 are directed to products of manufacture comprising embryonic stem cells and serum-free medium and a eukaryotic cell culture medium supplement.

While the specification is enabling for methods of culturing the embryonic stem cell lines, D3 ES cell line, the two mouse strain 129 ES cell lines, E14 and R1, and a non-129 ES cell line, TT2, under defined culture conditions as set forth in Examples 1 through 5, the specification is not enabling for culturing any embryonic stem cell in the absence of a feeder layer utilizing the broadly claimed medium supplements, nor is the specification enabling for methods of differentiating embryonic stem cells, methods of isolating embryonic stem cells from blastocysts, or methods of producing recombinant proteins as claimed. The specification discloses culturing the above-mentioned embryonic stem cell lines in a particular serum-free formulation (see Examples 1 through 5, and Tables 1 and 3). Cells cultured under these specific conditions are capable of expansion, *in vitro*, and display normal phenotypic and morphologic characteristics. The specification also provides an example of germ-line competence with R1 ES cells grown under these specific conditions (see, e.g., Example 8).

However, with regard to the broadly claimed embryonic stem cells, at the time of filing, the state of the art is such that generation of ES cells, i.e., cells which retain their totipotential capacity and are able to generate cells of all lineages, including germline, after being introduced into host a blastocyst, is neither routine nor predictable in species other than mice. Keller (Current Opinion in Cell Biology, 1995) teaches that ES cells are totipotent lines derived from the inner cell mass of developing blastocysts. When maintained on embryonic fibroblasts in culture, ES cells retain their totipotential capacity and are able to generate cells of all lineages, including germline, after being introduced into a host blastocyst (see page 862, left column, first paragraph).

However, at the time of filing, the state of the art is such that generation of ES cells, i.e., cells which retain their totipotential capacity and are able to generate cells of all lineages, including germline, after being introduced into host a blastocyst, is neither routine nor predictable in species other than mice. Bradley (Biotechnology, 1992) teaches that while a number of reports have been made claiming isolation of ES cells from farm animals, the description of these cell lines is yet to be supported by the demonstration that they can proliferate and differentiate in an embryo, *in vivo*, contributing to somatic tissues or germ cells (see page 53, right column, last paragraph bridging page 54). Moreover, Seamark (Reproductive Fertility and Development, 6:653-657, 1994) discloses that totipotency for ES cell technology in many livestock species has not been demonstrated (see, e.g., Abstract). Similarly, Matsui *et al.* (Cell, 1992) disclose that while it is well established that pluripotential stem cells, i.e., those originally termed ES cells, can be derived from the epiblast of blastocysts in culture, it is crucial to determine whether blastocyst-derived stem cells differ in their full range of developmental potencies and properties, such as genomic imprinting (see page 845, right column, 2nd paragraph, under "Reprogramming...", and page 846, left column, second full paragraph). In view of the lack of guidance in the specification with regard to the process of obtaining embryonic stem cells with the requisite "embryonic stem cell properties", the use of the cells in the claimed cell culture method and the claimed products of manufacture is not enabled.

The claims are also non-enabled as they broadly recite supplement ingredients to be used in the claimed culture methods and the claimed products of manufacture, i.e., supplement ingredients which are capable of supporting growth of embryonic stem cells. While the specification discloses a particle medium formulation containing the supplement ingredients at specific concentrations, and provides evidence that such a medium formulation supports embryonic stem cell growth/differentiation, the specification does not disclose or provide evidence that the broadly claimed supplement ingredients at any concentration range support the growth/differentiation of embryonic stem cells. The specification fails to provide an enabling disclosure for how to make and use any and all combinations of media supplements, media

formulations, and media useful for the claimed methods as the specification does not provide adequate guidance for the selection of appropriate serum-free medium supplements that would support the expansion/differentiation of embryonic stem cells as required by the claims. While the specification provides an explicit teaching regarding the ingredients that could be used to make a medium appropriate to practice the claimed invention, the specification does not provide guidance as to which ingredients can be excluded from the formulation, and whether the concentrations of the remaining ingredients need optimization as a result of the exclusion of particular ingredients.

Moreover, the state of the art at the time of filing indicates the difficulties of culturing embryonic stem cells. For example, Baribault *et al.* (Mol. Biol. Med., 1989) disclose that culture conditions and passage number may influence the ability of ES cells to give rise to germ-line chimeras. Different conditions might induce changes in karyotype, or culture of ES cells for many passages may select for the cells with a higher growth rate and teratocarcinoma-like phenotype. Baribault *et al.* also teach that when embryonal carcinoma cells are re-injected into mouse blastocysts, they infrequently produce germ-line chimeras but often induce tumors. A further consideration of culturing ES cells under conditions for maintaining an undifferentiated state is the stability of the stem cell phenotype, which should be monitored using cell surface markers which identify the embryonic phenotype, as well as regular karyotyping (see page 485, left column, first paragraph).

Taken together, the state of the art at the time of filing establishes the unpredictability of obtaining embryonic stem cells and maintaining such cells in culture such that the cells retain the requisite "stem cell characteristics", i.e., the ability to proliferate and differentiate in an embryo, *in vivo*, contributing to somatic tissues or germ cells. Inasmuch as the specification only discloses one particular medium formulation which supports the growth of specific embryonic stem cell lines, D3 ES cell line, the two mouse strain 129 ES cell lines, E14 and R1, and a non-129 ES cell line, TT2, such that said cells maintain a stable phenotype and retain their totipotential capacity such that they are able to generate cells of all lineages, including germline, after being introduced

into a host blastocyst, one of skill in the art would not have a high expectation of making and using the invention as claimed without undue experimentation.

Claims 117-121, directed to differentiating the cells in serum-free culture are also not enabled as the specification clearly indicates, on page 44, that when the cells are plated on electrostatically charged plastic and allowed to attach, the embryoid bodies would not attach without the addition of 1% FBS to supply undefined attachment factors. Once attached, the differentiated cells that grew out of the embryoid bodies were quite different than those seen in FBS-supplemented medium. While the specification indicates that cells can be induced to differentiate to at least cardiac cells, it is apparent from the specification that serum is required to effect differentiation. Thus, in view of the teachings in the specification, and the absence of guidance as to serum-free ingredients which can be used to replace the 1% FBS, one of skill in the art would not have had a high expectation of successfully differentiating embryonic stem cells under serum-free conditions without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 91-104, and 108-126 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 91, 98-103, 122, and 123 are rendered vague and indefinite by the phrase "is capable of" as it is unclear under which conditions the serum-free medium and/or supplements have the capacity to support the growth of embryonic stem cells. Moreover, the phrase "is capable of" is not a positive limitation.

Claims 108, 109, and 111 are rendered vague and indefinite by the phrase "controlling or preventing" as it is unclear if applicants are using the terms interchangeably or if there are distinct

culture conditions which allow for the control (rate?) of differentiation compared to culture conditions which prevent differentiation. Clarification is requested.

Claims 117 and 118 are rendered vague and indefinite by the phrase "or changing culture conditions to induce differentiation" as it is unclear how the culture conditions should be changed such that differentiation is induced.

Claim 124 is rendered vague and indefinite by the phrase "recombinant protein embryonic stem cells" as this does not appear to be an art-recognized embryonic stem cell. Applicants should amend the claim to "A method of producing a recombinant protein in" or "A method of producing recombinant proteins in" to overcome this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 101 is rejected under 35 U.S.C. 102(b) as being anticipated by the SIGMA Chemical Company Catalog (1994).

The SIGMA Chemical Company Catalog discloses serum-free supplements such as, insulins, albumins, vitamins, amino acid solutions, apo- and holo-transferrins, oxidation-reduction agents, collagen precursors, and minerals (see, e.g., pages 582, 993, 994, 1510-1515, and 1518-1529), each of which is in a container.

As the products of manufacture disclosed in the SIGMA Chemical Company Catalog contain the same ingredients as those claimed, the disclosure in the SIGMA Chemical Company Catalog anticipates the claimed invention.

Claim 101 is rejected under 35 U.S.C. 102(b) as being anticipated by the GIBCOBRL LIFE TECHNOLOGIES Catalogue (1993-1994).

The GIBCOBRL LIFE TECHNOLOGIES Catalogue discloses containers comprising serum-free supplements such as amino acids, hydroxyproline, AlbuMax I and II, vitamins, insulin, transferrin, and trace elements (see, e.g., pages 4-10, 4-19, and 4-41, 4-45, 4-46, and 4-53 to 4-56). Note that one of the disclosed vitamins, DL-α-tocopherol, is also an antioxidant.

As the products of manufacture disclosed in the GIBCOBRL LIFE TECHNOLOGIES Catalogue contain the same ingredients as those claimed, the disclosure in the GIBCOBRL LIFE TECHNOLOGIES Catalogue anticipates the claimed invention.

Claims 102 and 103 are rejected under 35 U.S.C. 102(b) as being anticipated by Ponting (U.S. Patent No. 5,405,772, 1995).

The claims are directed to a product of manufacture comprising a first container means containing a serum-free basal cell culture medium supplemented with a serum-free, eukaryotic cell culture medium supplement which can comprise one or more ingredients selected from albumins or albumin substitutes, one or more amino acids, one or more vitamins, one or more transferrins or transferrin substitutes, one or more antioxidants, one or more insulins or insulin substitutes, one or more collagen precursors, and one or more trace elements.

Ponting discloses a product of manufacture containing a basal cell culture medium supplemented with a serum-free eukaryotic cell culture medium supplement comprising serum albumin, transferrin, amino acids, which are inherently precursors of collagen, vitamins, and insulin (see, e.g., columns 12 and 13).

As the product of manufacture disclosed by Ponting contains the same ingredients as those claimed, the disclosure of Ponting anticipates the claimed invention.

Claims 102 and 103 are rejected under 35 U.S.C. 102(b) as being anticipated by Cleveland *et al.* (U.S. Patent No. 4,767,704, 1988).

The claims are directed to a product of manufacture as described in the above 35 U.S.C. 102(b) rejection.

Cleveland *et al.* disclose a container comprising supplemented basal medium, which is serum-free, comprising amino acids, which are inherently precursors of collagen, vitamins, trace minerals (see, e.g., Example 1, columns 12-14, and claims 1-23), transferrin, and insulin (see, e.g., column 13, lines 61-62).

As the product of manufacture disclosed by Cleveland *et al.* contains the same ingredients as those claimed, the disclosure of Cleveland *et al.* anticipates the claimed invention.

Claims 101-103 are rejected under 35 U.S.C. 102(b) as being anticipated by Ramos *et al.* (WO 92/05246, 1992).

Ramos *et al.* disclose the supplements, bovine serum albumin, bovine insulin, and bovine transferrin, which are added to a serum-free basal medium (see, e.g., pages 4, 6, 7). Transferrin substitutes, such as ferric citrate or ferrous sulfate, can also be used as supplements (see, e.g., page 4, lines 23-29). In addition, Ramos *et al.* disclose a method of formulating a serum-free basal medium by admixing ingredients such as vitamins, minerals, fatty acids, amino acids, and trace elements (see, e.g, pages 6-8).

Thus, the disclosure of Ramos *et al.* anticipates applicants' claims.

Claim 104 is rejected under 35 U.S.C. 102(b) as being anticipated by the SIGMA Chemical Company Catalog (1994).

The SIGMA Chemical Company Catalog discloses a container comprising the serum-free supplements insulin, transferrin and sodium selenite, a container comprising a vitamins solution, and a container containing transferrin, all of which are in frozen state, i.e., "-0°C" (see, e.g., page 1512, Catalog #I 1884, page 1513, Catalog # M 6895, and page 1514, Catalog # T 8158).

As the products of manufacture disclosed in the SIGMA Chemical Company Catalog contain the same ingredients as those claimed, the disclosure in the SIGMA Chemical Company Catalog anticipates the claimed invention.

Claim 104 is rejected under 35 U.S.C. 102(b) as being anticipated by the GIBCOBRL LIFE TECHNOLOGIES Catalogue (1993-1994).

The GIBCOBRL LIFE TECHNOLOGIES Catalogue discloses serum-free supplements such as amino acid solutions, vitamin solutions, and insulin, which are in a frozen state (see, e.g., page 4-19, Catalog Nos. 21135-017 and 21135-025, page 4-44, Catalog Nos. 18125-021, 18125-039, 18135-012 and 18135-020, and page 4-55, Catalog No. 21040-019).

As the products of manufacture disclosed in the GIBCOBRL LIFE TECHNOLOGIES Catalogue contain the same ingredients as those claimed, the disclosure in the GIBCOBRL LIFE TECHNOLOGIES Catalogue anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 101-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleveland *et al.* (U.S. Patent No. 4,767,704, 1988), or Ponting (U.S. Patent No. 5,405,772, 1995), or Ramos (WO 92/05246, 1992), each taken with Maurer (in, "Animal Cell Culture, A Practical Approach", pages 13-31, 1986), and either the SIGMA Chemical Company Chemical Catalog (1994), or the GIBCOBRL LIFE TECHNOLOGIES Catalogue (1993-1994).

The claims are directed to products of manufacture comprising serum-free supplements or a serum-free basal medium containing serum-free supplements.

Cleveland *et al.* disclose a container comprising supplemented basal medium, which is serum-free, comprising amino acids, which are inherently precursors of collagen, vitamins, trace minerals (see, e.g., Example 1, columns 12-14, and claims 1-23), transferrin, and insulin (see, e.g., column 13, lines 61-62).

Alternatively, Ponting discloses a product of manufacture containing a basal cell culture medium supplemented with a serum-free eukaryotic cell culture medium supplement comprising serum albumin, transferrin, amino acids, which are inherently precursors of collagen, vitamins, and insulin (see, e.g., columns 12 and 13).

Alternatively, Ramos *et al.* disclose the supplements, bovine serum albumin, bovine insulin, and bovine transferrin, which are added to a serum-free basal medium (see, e.g., pages 4, 6, 7). Transferrin substitutes, such as ferric citrate or ferrous sulfate, can also be used as supplements (see, e.g., page 4, lines 23-29). In addition, Ramos *et al.* disclose a method of formulating a serum-free basal medium by admixing ingredients such as vitamins, minerals, fatty acids, amino acids, and trace elements (see, e.g, pages 6-8).

The references do not enclose all potential combinations of the claim-designated serum-free supplement ingredients which can be added to serum-free basal medium formulations. However, Maurer teaches commercially available serum-free media and supplements which are available for optimizing mammalian cell cultures (see page 28-29, and Table 3) including the use of serum-substitutes, such as insulin, transferrin, growth factors, and hormones, for replacing the serum, as well as other supplements such as trace elements (see, e.g., page 25). Maurer provides

motivation for developing supplemented serum-free medium formulations in that Maurer discloses that using serum in cell culture has distinct disadvantages including that 1) for most cells, serum is not the physiological fluid which they contact in the original tissue from which they are derived, that 2) serum is potentially toxic, that 3) large batch-to-batch variations of sera require extensive serum screening, which is time consuming and costly, and that 4) serum may contain inadequate levels of cell-specific growth factors, which have to be supplemented (see, e.g., pages 20 and 21, under the section entitled "Distinct Disadvantages of using Serum in Cell Culture"). Furthermore, Maurer discloses the advantages of using serum-free media including 1) improved reproducibility between cultures, 2) reduced risk of contamination, 3) easier purification of culture products, etc. (see, e.g., pages 15 and 20, under the section entitled "Potential Advantages of using Low-serum and Serum-free Media). Thus, modifying the formulations disclosed by Cleveland *et al.*, Ponting, or Ramos *et al.* by altering the different types of nutrient supplements in serum-free medium formulations would have been obvious and well within the purview of the skilled artisan for the purpose of optimizing serum-free eukaryotic cell medium formulations, in view of the teachings of Maurer.

The references do not disclose that the products of manufacture are in a frozen state. However, both the SIGMA Chemical Company Catalog (see, e.g., page 1512, Catalog #I 1884, page 1513, Catalog # M 6895, and page 1514, Catalog # T 8158) and the GIBCOBRL LIFE TECHNOLOGIES Catalogue (see, e.g., page 4-19, Catalog Nos. 21135-017 and 21135-025, page 4-44, Catalog Nos. 18125-021, 18125-039, 18135-012 and 18135-020, and page 4-55, Catalog No. 21040-019) provide cell culture medium supplements in the frozen state. Moreover, both the SIGMA Chemical Company Catalog and the GIBCOBRL LIFE TECHNOLOGIES Catalogue indicate that maintaining the products of manufacture in a frozen state ensures the quality of the products (see, e.g., page 5, under Shipping, and page 7, under Storage Temperature, in the SIGMA Chemical Company Catalog, and page 1-3 of the GIBCOBRL LIFE TECHNOLOGIES Catalogue).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the products of manufacture comprising cell culture medium and medium supplements of Cleveland *et al.*, Ponting, or Ramos *et al.* by altering the types of supplements to be included in the basal medium formulation, as discussed by Maurer, and further, providing the products of manufacture in the frozen state in view of the disclosures in the SIGMA Chemical Company Catalog, or alternatively, in the GIBCOBRL LIFE TECHNOLOGIES Catalogue, that serum-free medium supplements are shipped frozen and should be stored frozen to insure quality or to sustain optimal performance of the products. One of skill in the art would have been motivated to provide a product of manufacture containing a combination of serum-free supplements, or a combination of serum-free basal medium and serum-free supplements optimized for growing particular types of eukaryotic cells in view of the disadvantages of using serum and the advantages of using serum-free medium formulations for culturing eukaryotic cells, as disclosed by Maurer, and to freeze such formulations/supplements for shipping and storage as it is well known that maintaining compositions containing nutrients in the frozen state enhances the stability of such compositions, as taught in the Sigma Chemical Company Catalog and the GIBCOBRL LIFE TECHNOLOGIES Catalogue.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to John LeGuyader, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-0447. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via

the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Janet M. Kerr, Ph.D.
Patent Examiner
Group 1600

DEBORAH J. CLARK
PATENT EXAMINER